Poster No. P046

Post hoc analysis to evaluate the effects of subcutaneous interferon beta-1a in subgroups of patients from the PRISMS study with early-onset versus late-onset disease

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INTRODUCTION

- The occurrence of relapses in relapsing multiple sclerosis (RMS) can be irregular, coupled with slow and gradual disease progression. As such, clinical trials of disease-modifying drugs for RMS generally assess clinical and radiologic endpoints over 2 years or longer.[1,2]
- Studies have shown that older age at MS onset is an independent risk factor for disability progression.[3]
- The 2-year PRISMS (Prevention of Relapses and disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) study found that subcutaneous interferon β-1a (sc IFN β-1a) three times weekly (tiw) significantly reduced relapses and active T2 lesions in patients with RMS at 2 years compared with placebo, while also significantly delaying disability progression.[4]
- Analysis of 1-year PRISMS data found that the treatment benefits of sc IFN β-1a in subgroups of patients aged <40 and ⩾40 years were consistent with the overall population.[5]

OBJECTIVES

- To assess the effects of sc IFN β-1a 44 µg tiw after 2 years of treatment in patients with RMS, stratified by age and time since disease onset.
- To determine if 2-year PRISMS data are consistent with a previous 1-year subgroup analysis.

METHODS

- *Post hoc* analysis of PRISMS stratified patients by age (<40 years vs ⩾40 years) and time since MS onset (<4 years vs ⩾4 years; defined by the time of first symptom or exacerbation).
- Treatment effects of sc IFN β-1a 44 µg tiw on clinical and magnetic resonance imaging (MRI) endpoints were assessed over 2 years and compared with Year 1 results. The same statistical method and efficacy endpoints were used as for the 1-year analysis:
  - Relapses: annualized relapse rate (ARR), time to first exacerbation up to 2 years, and proportion of patients free of exacerbations at 2 years.
  - 3-month confirmed Expanded Disability Status Scale (EDSS) progression: time to confirmed progression up to 2 years and proportion of patients free from progression at 2 years.
  - MRI: number of T2 active lesions up to 2 years.
- Relative treatment effects of sc IFN β-1a 44 µg tiw versus placebo were examined using rate, hazard and odds ratios, and their associated 95% confidence intervals.

RESULTS

- Demographic and baseline characteristics for patients enrolled in PRISMS stratified by age and time since MS onset are shown in **Table 1** and **Table 2**, respectively.

Relapse endpoints at 2 years

- In patients aged ⩾40 years (n=55), treatment with sc IFN β-1a tiw was associated with a significant reduction in clinical measures versus placebo (n=52) over 2 years, including a 33% reduction in ARR (**Figure 1**; p=0.003).
- Similar significant results were observed in the subgroup of patients aged <40 years (n=129) treated with sc IFN β-1a tiw versus placebo (n=135). ARR was also reduced by 33% (**Figure 1**; p<0.001).

Table 1. PRISMS demographic and baseline characteristics – age subgroups

Characteristic	Placebo			sc IFN β-1a 44 µg tiw		
	<40 years (n=135)	⩾40 years (n=52)	Overall ITT (n=187)	<40 years (n=129)	⩾40 years (n=55)	Overall ITT (n=184)
Age, years	31.1 (5.2)	44.1 (2.8)	34.7 (7.5)	31.2 (5.6)	44.7 (3.0)	35.2 (7.9)
Sex, female, %	75	77	75	68	62	66
EDSS	2.26 (1.19)	2.86 (1.18)	2.43 (1.21)	2.39 (1.21)	2.67 (1.40)	2.48 (1.27)
Number of relapses in prior year	3.1 (1.3)	2.8 (1.0)	3.0 (1.3)	3.1 (1.2)	2.7 (0.8)	3.0 (1.1)
Time since MS onset, years	5.2 (4.1)	8.5 (5.8)	6.1 (4.8)	7.0 (5.2)	9.8 (7.8)	7.8 (6.3)

Data are presented as mean (standard deviation) unless otherwise indicated.
EDSS, Expanded Disability Status Scale; **IFN**, interferon; **ITT**, intention to treat; **MS**, multiple sclerosis; **sc**, subcutaneous; **tiw**, three times weekly.

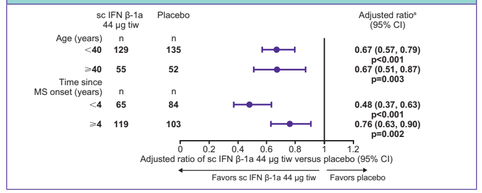
Table 2. PRISMS demographic and baseline characteristics – time since MS onset subgroup

Characteristic	Placebo			sc IFN β-1a 44 µg tiw		
	<4 years (n=84)	⩾4 years (n=103)	Overall ITT (n=187)	<4 years (n=65)	⩾4 years (n=119)	Overall ITT (n=184)
Age, years	32.9 (7.4)	36.2 (7.2)	34.7 (7.5)	32.5 (8.4)	36.7 (7.2)	35.2 (7.9)
Sex, female, %	75	76	75	66	66	66
EDSS	2.23 (1.09)	2.59 (1.28)	2.43 (1.21)	1.92 (1.23)	2.78 (1.19)	2.48 (1.27)
Number of relapses in prior year	3.3 (1.4)	2.9 (1.1)	3.0 (1.3)	3.1 (1.2)	2.9 (1.0)	3.0 (1.1)
Time since MS onset, years	2.4 (0.8)	9.2 (4.5)	6.1 (4.8)	2.3 (0.8)	10.8 (5.9)	7.8 (6.3)

Data are presented as mean (standard deviation) unless otherwise indicated.
EDSS, Expanded Disability Status Scale; **IFN**, interferon; **ITT**, intention to treat; **MS**, multiple sclerosis; **sc**, subcutaneous; **tiw**, three times weekly.

- A significant treatment benefit for sc IFN β-1a tiw versus placebo was shown regardless of time since MS onset, although this finding was more pronounced in the subgroup of patients with time since MS onset of <4 years (**Figure 1**, n=65 vs n=84; 52% reduction in ARR in the <4 years group vs 24% reduction in the ⩾4 years group; p<0.001 and p=0.002, respectively).

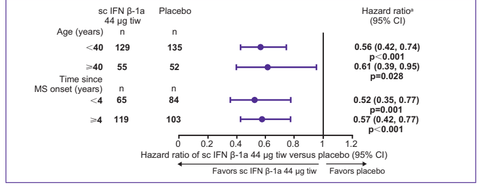
Figure 1. 2-year annualized relapse rate



Statistically significant results are highlighted in bold.
[a]Poisson model with treatment as factor, number of prestudy exacerbations as covariate, and log time on study as offset variable.
CI, confidence interval; **IFN**, interferon; **MS**, multiple sclerosis; **sc**, subcutaneous; **tiw**, three times weekly.

- In patients aged ⩾40 years, there was a significant reduction of 39% in time to first exacerbation with sc IFN β-1a versus placebo (**Figure 2**, p=0.028).
- A 44% reduction in time to first exacerbation (**Figure 2**, p<0.001) was found in patients <40 years with sc IFN β-1a versus placebo.
- Time to first exacerbation up to 2 years was significantly reduced in patients with time since MS onset <4 years and ⩾4 years (**Figure 2**, p=0.001 and p<0.001, respectively).

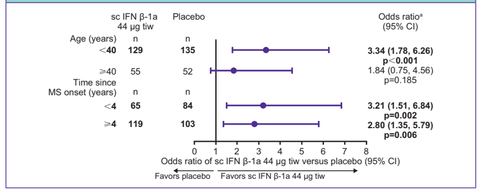
Figure 2. Time to first exacerbation up to 2 years



Statistically significant results are highlighted in bold.
[a]Cox proportional hazards model with treatment as factor and number of prestudy exacerbations as covariate.
CI, confidence interval; **IFN**, interferon; **MS**, multiple sclerosis; **sc**, subcutaneous; **tiw**, three times weekly.

- A significantly greater proportion of patients <40 years (but not ⩾40 years) was free of exacerbations at 2 years with sc IFN β-1a treatment compared with placebo (**Figure 3**; p<0.001).
- The proportion of patients free of exacerbations at 2 years was significantly higher with IFN β-1a in both the <4 years and ⩾4 years since MS onset groups (**Figure 3**; p=0.002 and p=0.006, respectively).

Figure 3. Proportion of patients free of exacerbations at 2 years

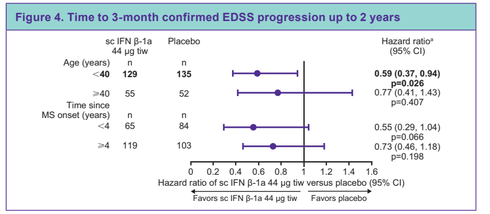


Statistically significant results are highlighted in bold.
[a]Logistic model with treatment as factor and number of prestudy exacerbations as covariate.
CI, confidence interval; **IFN**, interferon; **MS**, multiple sclerosis; **sc**, subcutaneous; **tiw**, three times weekly.

Disability progression at 2 years

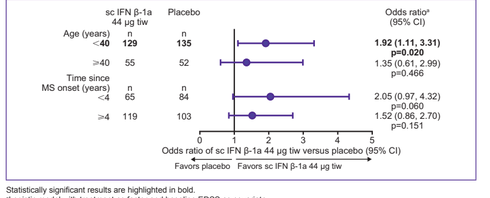
- Significant treatment benefits were seen in time to 3-month confirmed EDSS progression in patients aged <40 years, which were not observed in patients aged ⩾40 years (**Figure 4**; p=0.026).
- Similar significant results for patients aged <40 years were observed in the proportion of patients free of 3-month confirmed EDSS progression at 2 years (**Figure 5**; p=0.020).
- The time since MS onset subgroups were found to not be significantly affected.

Figure 4. Time to 3-month confirmed EDSS progression up to 2 years



Statistically significant results are highlighted in bold.
[a]Cox proportional hazards model with treatment as factor and baseline EDSS as covariate.
CI, confidence interval; **EDSS**, Expanded Disability Status Scale; **IFN**, interferon; **MS**, multiple sclerosis; **sc**, subcutaneous; **tiw**, three times weekly.

Figure 5. Proportion of patients free of 3-month confirmed EDSS progression at 2 years

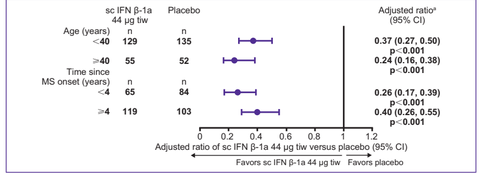


Statistically significant results are highlighted in bold.
[a]Logistic model with treatment as factor and baseline EDSS as covariate.
CI, confidence interval; **EDSS**, Expanded Disability Status Scale; **IFN**, interferon; **MS**, multiple sclerosis; **sc**, subcutaneous; **tiw**, three times weekly.

MRI endpoints at 2 years

- The number of T2 active lesions was significantly reduced in both age subgroups with sc IFN β-1a treatment versus placebo; 76% (p<0.001) and 63% (p<0.001) reductions in patients ⩾40 years and <40 years, respectively (**Figure 6**).

Figure 6. Number of T2 active lesions up to 2 years



Statistically significant results are highlighted in bold.
[a]Poisson model with treatment as factor, number of prestudy exacerbations as covariate, and log time on study as offset variable.
CI, confidence interval; **IFN**, interferon; **MS**, multiple sclerosis; **sc**, subcutaneous; **tiw**, three times weekly.

Limitations

- Subgroups were defined *post hoc* and, as such, were not powered for the analysis.
- The number of patients in the ⩾40 years age group was lower compared with the <40 years cohort.

CONCLUSIONS

- **Treatment benefit of sc IFN β-1a tiw versus placebo was demonstrated in the older patient subgroup (⩾40 years) for 2-year ARR and time to first exacerbation up to 2 years, along with MRI disease activity over 2 years. No benefit was seen on disease progression, with the known limitations of the analysis.**
- **Analyses of time since MS onset also showed that early initiation of MS treatment is associated with better clinical outcomes.**
- **Results were consistent with those of the 1-year efficacy findings, demonstrating that, in patient subgroups stratified by age and time since MS onset, the treatment benefits of sc IFN β-1a tiw versus placebo on relapse and MRI endpoints at 2 years were consistent with the overall population.**

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